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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,436	08/13/2001	Mitra Tadayoni-Rebek	0942.5300001/RWE/AGU	6227

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,436	TADAYONI-REBEK ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/7/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-20,39 and 41-52* is/are pending in the application.

4a) Of the above claim(s) *44-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20,39,41-43 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 3/7/05, claims 16-20, 39, 41, 42, 48, 49 have been amended, claim 40 cancelled, and claims 50-52 added. Claims 6-20, 39, 41-52 are now pending. Claims 44-47 remain withdrawn from consideration.

Applicants' arguments filed 3/7/05 have been considered and found persuasive in part. The rejection of claims 16, 39, 40, 42, 43 as unpatentable over Aimoto (USP '958) is withdrawn.

Claims 16-20, 39, 41-43, 48-52 are examined in this Office action.

✧

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-20, 39, 41-43, 48-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There are two issues raised herein. The first concerns the recitation that the "label is not an amino acid". However, there does not appear to be descriptive support for this limitation. Applicants are requested to point to the page and line number where support can

be found.

The second issue concerns the recitation in (e.g.) claim 16 that a labeled molecule is ligated to a nucleic acid so as to form a peptide bond. For purposes of discussion, the following variables are defined below:

peptide-COSR = a peptide bearing a thioester

HS-DNA = an oligodeoxyribonucleic acid bearing a thiol group;

DNA-COSR = an oligodeoxyribonucleic acid bearing a thioester

HS-peptide = a peptide bearing a thiol group

Claim 16 (for example) encompasses the following two reactions:

peptide-COSR + HS-DNA → peptide-CONH-DNA

DNA-COSR + HS-peptide → DNA-NHCO-peptide

However, there does not appear to be descriptive support for either of them. Certainly, there is a suggestion that one could synthesize the following compound in which segment A is a peptide, and segment B is a polynucleic acid:

Segment A – L - Segment B

However, it does not appear that there is a description of reacting an oligoribonucleic acid or an oligodeoxyribonucleic acid with a peptide so as to form an amide bond between them,

while at the same time meeting the requirement that one of the two compounds bear a thioester, and the other a thiol. If applicants believe that support exists, applicants are requested to point out the location in the text.

✦

Claims 16-20, 39, 41-43, 48-52 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated above (§112, first paragraph "possession"), there appears to be no support for chimeric molecules which consist of a peptide or protein bonded, via amide linkage, to an oligoribonucleic acid or an oligodeoxyribonucleic acid. This ground of rejection is intended to make the point that, in addition to not describing such compounds, the specification does not enable them either. It is acknowledged that there is a body of literature on peptide nucleic acids. However, it does not appear that the specification makes any reference to such, and does not imply that they can be made in accordance with the claimed invention. Thus, the question becomes, how does one make and use chimeric peptide/nucleic acid conjugates in which an amide bond links the two? Certainly there is no shortage of literature on how to use polynucleotides, and separately, how to use peptides and proteins. But there is no evidence of record that one can use the chimeric molecules referred to above (in which an amide bond links the two). In attempting to

extrapolate from the properties and behaviors of peptides to peptide/polynucleotide conjugates, "unpredictable" results are obtained.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As it happens, there are no "working examples" which show the skilled artisan how to use such peptide/nucleic acid chimeras, and there is no evidence that the prior art shows one how to use the same.

In accordance with the foregoing, "undue experimentation" would be required to practice the claimed invention.

✧

Claims 17, 18, 20, 48, 52 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

> Claim 17 is drawn to a method of preparing a "marker molecule composition". A composition must contain at least two compounds. Claim 17 encompasses the possibility that two or more compounds are produced by the recited method; however, the claim does not explicitly require that two or more compounds be produced. Suppose that step (c) is not carried out, and that just one labeled peptide is produced.

The labeled peptide is a single compound, not a composition. The question then is, for the chemist who is in possession of this single peptide, what else must he do or add so that he is finally in possession of a composition? The same issue applies in the case of claims 20, 48 and 52.

✦

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 16, 17, 19, 20, 39, 42, 43, 51, 52 are rejected under 35 U.S.C. §103 as being unpatentable over Canne (USP 6,326,468).

As indicated previously, Canne discloses a peptide ligation method in which a peptide bearing an N-terminal cysteine is reacted with another peptide bearing a C-terminal thioester group to form a larger peptide. Reaction schemes are summarized, e.g., in figures 1, 16, 20 and 21. As is evident, the coupling process can be performed more than once. Also suggested (col 14,

line 60+) is that the "first peptide segment" or the "incoming peptide segment" can be used in excess.

In response to the foregoing, applicants have amended the claims to recite two limitations, neither of which was previously present. The first is to require that the label is a chromophore, fluorophore or UV absorbing group. The second is to recite that that the label is not an amino acid. However, these limitations are not effective to overcome this ground of rejection. The first point is that the side chains of phenylalanine, tryptophan, and tyrosine exhibit some absorption in the UV. The extinction coefficient may not be large, but for a peptide with many such groups, the UV absorption is readily measurable. Further, tryptophan is weakly fluorescent.

The second limitation that was not previously present is, as indicated, that the label is not an amino acid. However, this particular limitation has little effect. The reason is that the limitation is readily circumvented for the case where the "label" is a peptide that consists of at least two amino acids. Consider, for example, the procedure described at col 22, line 36+. This is a procedure for preparation of the peptide of SEQ ID NO:4. This peptide was obtained by a sequential process of ligating MIF(1-59), MIF(60-80) and MIF(81-115). But as is evident, each of these three fragments contains at least one phenylalanine, tyrosine, or tryptophan. Thus, each of MIF(1-59), MIF(60-80) and MIF(81-115) is a "labeled" molecule, and moreover, each is

labeled with a substitutent that is UV-absorbing. In preparing each of MIF(1-59), MIF(60-80) and MIF(81-115), one is "labeling" a molecule. The molecule that is being labeled is a peptide, and the "label" itself is a peptide. That is, tryptophan (for example) is itself a UV-absorbing label. The tripeptide Gly-Trp-Gly (for example) is also a UV-absorbing label. And the following peptide is a UV-absorbing label; it is also a molecule bearing a label: W-N-N-S-T-F-A. As indicated above, the exclusion in the last line of claim 16 is directed solely toamino acids, and does not include peptides. As such, it has no effect on the basis of this rejection.

The rejection is maintained.

✧

Claims 16, 17, 19, 20, 39, 42, 43, 51, 52 are rejected under 35 U.S.C. §103 as being unpatentable over Kent (USP 6,307,018).

As indicated previously, Kent discloses (e.g., figure 1) a coupling procedure in which a "peptide 1" bearing a thioester group is reacted with a "peptide 2" bearing an N-terminal sulfhydryl moiety. As indicated above (the §103 over Canne), dipeptides, tripeptides, tetrapeptides (etc.) that contain any of Phe, Trp or Tyr contain a UV-absorbing group, and at the same time, sidestep the exclusion of the label being an amino acid. As it happens, at least one of the peptides disclosed in Kent contains a phenylalanine. But in addition, the disclosed method is that of synthesizing <u>any</u> peptide. As applicants no doubt recognize, there are hundreds of thousands of peptides known in the literature which contain at least one of these

amino acids.

The rejection is maintained.

✧

Claims 16, 17, 19, 20, 39, 42, 43, 51, 52 are rejected under 35 U.S.C. §103 as being unpatentable over Kent (USP 6,476,190).

Kent discloses (e.g., figure 1) a ligation procedure in which a C-terminal thioester of a "first" peptide is reacted with a "second" peptide, wherein the second peptide bears an N-terminal bromoacetyl group. The result is a new peptide which itself contains a thioester bond (at the point of ligation).

As indicated above, the new limitations are not effective to overcome this ground of rejection. The peptide disclosed in the reference contains all three of the following UV-absorbing amino acids: Phe, Trp and Tyr.

The rejection is maintained.

✧

Claims 16, 17, 19, 20, 39, 42, 43, 51, 52 are rejected under 35 U.S.C. §103 as being unpatentable over Canne (USP 6,326,468) in view of any of the following: Stamler (USP 5593876) or McKernan (USP 5,698,521) or DeBaryshe (USP 5,713,364) or Kim (USP 5,662,917) or Kittrell (USP 5,562,100).

The teachings of Canne are indicated above. Canne does not teach that the side chains of phenylalanine, tryptophan, and tyrosine exhibit some absorption in the UV, and does not

teach that tryptophan is fluorescent. The secondary references, however, teach these properties of the amino acids in question. Relevant passages are as follows:

- Stamler discloses (col 6, line 55 and figures 21d-21e) that tyrosine absorbs in the UV.
- McKernan discloses (col 19, line 38+) that tryptophan absorbs in the UV.
- DeBaryshe discloses (col 1, line 62+) that tryptophan is fluorescent.
- Kim discloses (col 4, line 53+) that Tyr, Phe and Trp all absorb in the UV
- Kittrell discloses (col 5, line 31+) that tryptophan is fluorescent.

Thus, a dipeptide subsequence that contains Trp, Phe or Tyr will be a UV-absorbing or fluorescent label, while at the same time circumventing the exclusion of being an amino acid. Similarly, a tripeptide or tetrapeptide subsequence that contains one of the indicated amino acid will be a "label" in accordance with the claims, but without falling within the exclusion that is recited in the last line of the claim.

The claims are thus rendered obvious.

✦

Claims 16, 17, 19, 20, 39, 42, 43, 51, 52 are rejected under 35 U.S.C. §103 as being unpatentable over Kent (USP 6,307,018) in view of any of the following: Stamler (USP 5593876) or McKernan (USP 5,698,521) or DeBaryshe (USP 5,713,364) or Kim (USP 5,662,917) or Kittrell (USP 5,562,100).

The teachings of Kent were indicated previously. Kent also discloses peptide sequences that contain at least one of Phe, Tyr and Trp. In addition, the process disclosed in the reference is intended for any peptide; there are countless peptides known that contain at least one of the three amino acids in question. Kent does not teach that the side chains of phenylalanine, tryptophan, and tyrosine exhibit some absorption in the UV, and does not teach that tryptophan is fluorescent. The secondary references, however, teach these properties of the amino acids in question.

Thus in preparing the peptide precursors (that contain one of Phe, Tyr and Trp), one is meeting step (a) of the instant claims. And Kent clearly teaches the ligation step. Thus, the claims are rendered obvious.

✧

Claims 16, 17, 19, 20, 39, 42, 43, 51, 52 are rejected under 35 U.S.C. §103 as being unpatentable over Kent (USP 6,476,190) in view of any of the following: Stamler (USP 5593876) or McKernan (USP 5,698,521) or DeBaryshe (USP 5,713,364) or Kim (USP 5,662,917) or Kittrell (USP 5,562,100).

The teachings of Kent were indicated previously. Kent also discloses peptide sequences that contain at least one of Phe, Tyr and Trp. In addition, the process disclosed in the reference is intended for any peptide; there are countless peptides known that contain at least one of the three amino acids in question. Kent does not teach that the side chains of phenylalanine, tryptophan, and tyrosine exhibit some absorption in the UV, and does not

teach that tryptophan is fluorescent. The secondary references, however, teach these properties of the amino acids in question.

Thus, in preparing the peptide precursors (that contain once of Phe, Tyr and Trp), one is meeting step (a) of the instant claims. And Kent clearly teaches the ligation step. Thus, the claims are rendered obvious.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

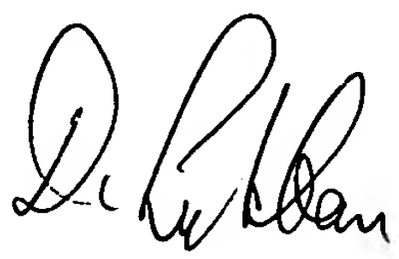
A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



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